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LOW-CHARGE STATE AMS FOR HIGH THROUGHPUT ^{14}C QUANTIFICATION

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ABSTRACT

Accelerator mass spectrometry (AMS) quantifies attomole (10^{-18}) amounts of ^{14}C in milligram sized samples. This sensitivity is used to trace nutrients, toxins and therapeutics in humans and animals at less than $\mu\text{g/kg}$ doses containing 1-100 nCi of ^{14}C . Widespread use of AMS in pharmaceutical development and biochemical science has been hampered by the size and expense of the typical spectrometer that has been developed for high precision radiocarbon dating. The precision of AMS can be relaxed for biochemical tracing, but sensitivity, accuracy and throughput are important properties that must be maintained in spectrometers designed for routine quantification. We are completing installation of a spectrometer that will maintain the high throughput of our primary spectrometer but which requires less than 20% of the floor space and of the cost. Sensitivity and throughput are kept high by using the LLNL intense cesium sputter ion source with solid graphitic samples. Resultant space-charge effects are minimized by careful modeling to find optimal ion transport in the spectrometer. A long charge-changing “stripper gas” volume removes molecular isobars at potentials of a few hundred kiloVolts, reducing the size of the accelerating component. Fast ion detectors count at high rates to keep a wide dynamic range for ^{14}C concentrations. Solid sample presentation eliminates the sample cross contamination that degrades accuracy and the effects of “memory” in the ion source. Automated processes are under development for conversion of liquid and solid biological samples to the preferred graphitic form for the ion source.

AMS FOR BIOMEDICAL ANALYSIS

Accelerator Mass Spectrometry (AMS) is a sensitive and selective isotope ratio spectrometer. Within a sample, the amount of the radioisotope (i.e., ^{14}C) is measured with a particle detector and compared to the level of the stable isotope (i.e., ^{13}C or ^{12}C) which is measured with a Faraday cup. Absolute quantification comes from normalizing the sample's isotopic ratio to that of similarly prepared and measured standards of a known isotopic ratio. Only atomic ions are measured; any molecular ions created in the ion source and subsequently injected into the accelerator are dissociated by high energy

collisions. AMS was initially developed for the geosciences and archeology as a means to date samples with radiocarbon. The development of AMS can be traced through conference proceedings (Wölfi et al. 1984, Gove et al. 1987, Yiou and Raisbeck 1990, Fifield et al. 1994, Jull et al. 1996), as well as in several reviews (Litherland 1980, Tuniz et al. 1998).

In the past decade, AMS has proven to be a very powerful tool in the biomedical sciences, including studies of nutrition, toxicology, pharmacokinetics and human carcinogenesis (Turteltaub and Vogel 2000). Because of the extreme sensitivity of AMS, it is possible to conduct radiolabel tracer studies without using “radioactivity”. The lifetime absorbed dose to a human participant due to ^{14}C decay from a radiolabelled pharmaceutical for AMS analysis would be at least 2-3 orders of magnitude less than the dose received from the commonly accepted risk of a 1 hour plane flight (Vogel 2000). Section 10CFR20.2005 of the U.S. government Consolidated Federal Register indicates that a material may be disposed of as nonradioactive if it contains ≤ 50 nCi of ^{14}C or ^3H per gram of animal tissue, averaged over the weight of the entire animal. This is much more than the 100 nCi doses typically given to a 70 kg human for biomedical AMS studies and ~ 100 times the upper limit on the range of ^{14}C levels that is directly measurable by AMS. The upper limit of ~ 1 pCi $^{14}\text{C}/\text{mg C}$ is to prevent detector overloading and ion source contamination that would prevent rapid sample sequencing. This upper limit can, of course, be extended through sample dilution.

Recent work (Suter et al. 1997) demonstrates the feasibility of ^{14}C analysis with low terminal voltages, resulting in a much smaller system, with its subsequent reduction in cost and increased ease of operation. At LLNL, we require, for biochemical AMS analysis, high throughput (>300 samples/day) with 1 attomole $^{14}\text{C}/\text{mg}$ carbon sensitivity at 3-5% precision. At the present time, all biomedical ^{14}C AMS analyses are conducted on the same spectrometer and often on the same ion source as used for highly sensitive and precise ^{14}C dating. Care must be taken to prevent the introduction of samples with extremely high ^{14}C levels that would result in unacceptable retention of ^{14}C in the ion source. A dedicated system for biochemical studies coupled with a fast particle detector would allow us to conservatively extend the upper limit by a factor of 10, providing a linear range over 5 orders of magnitude in a single analytical method. Our spectrometer, currently under construction, is centered around a National Electrostatics Corporation Model 3SDH-1 1-MV Pelletron Accelerator. A copy of the LLNL high-current cesium sputter ion source (Southon and Roberts 2000) will be used to generate intense ion beams from solid graphite samples. Careful modeling of the low energy beam line was conducted to best match our ion source emittance to the acceptance of the accelerator. The results of which were experimentally confirmed (Ognibene et al. 2000). We have constructed a 1200 sq. ft. room to house the spectrometer, as well as several laboratory work benches and are currently completing the final assembly.

AMS BIOSAMPLE REQUIREMENTS

The current Cs-sputter sources used in AMS require that biochemical samples be thermally and electrically conductive solids. Additionally, there must be chemical and physical equivalence for all carbon atoms in the samples and standards, as well as with

any carrier material added. Subsequently, all samples and standards to be analyzed via AMS are first combusted to CO₂ followed by the reduction of the CO₂ to graphite. This eliminates any sample matrix dependence on the measured isotopic ratio. Methods for preparing graphite for analysis by AMS in geochronology studies have been well developed (Vogel et al. 1989), but are not well suited for biomedical samples due to low throughput. Additionally, there is a high potential for cross contamination of the highly enriched samples from biomedical tracer studies, which may contain radiocarbon levels varying over 10 orders of magnitude.

There are several reasons why graphite is the preferred choice over CO₂ gas for a sample material. Graphite has no “vapor pressure” which makes sample handling easier, and controls contamination in the case of “hot” samples (>10 fmol ¹⁴C/mg C). One of the main features of the Cs-sputter ion source is the low memory effect between samples. This is especially important for biomedical samples whose ¹⁴C levels can vary greatly within an single experiment. This source has a relatively high ionization efficiency (1-10%) and can achieve high ion currents. This minimizes counting times while maintaining high precision and accuracy. In less time that it would take to switch and purge a gas sample, 1% precision on a graphite sample can be measured. Finally, graphite allows for remote sample production with the measurement conducted at a regional spectrometer.

With the expected high throughput of our spectrometer, we desire a sample preparation method that is able to process submilligram size biological samples into graphite at a similar rate. Such a system should be ≥90% efficient with <1% fractionation. Sample carryover must be limited to no more than 0.01% over six orders of magnitude in ¹⁴C concentration. Finally, the graphite formed must produce >0.5 μA C⁻ /μg ion beams. Graphite for AMS analysis from biological samples has been produced without contamination by using disposable manifolds in a sealed-tube process (Vogel 1992). This technique meets the requirements for our application except throughput is low. Development is underway to automate this process.

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